In an open-label pilot study, trigeminal nerve stimulation (TNS) was feasible and well tolerated and showed preliminary evidence of efficacy in children with ADHD.

**Background:** TNS is a noninvasive neuromodulation method currently under investigation for treatment of epilepsy and major depressive disorder. It is safe and well tolerated in adults but has not previously been investigated in pediatric patients. Treatment involves wearing a small stimulating device on the clothing and applying bilateral electrodes to the forehead to stimulate both V1 branches of the trigeminal nerve.

**Methods:** The present exploratory study was carried out in unmedicated patients, aged 7–14 years, with ADHD of at least moderate severity and high scores on both the inattentive and hyperactive/impulsive subscales of the ADHD Rating Scale IV (ADHD-RS-IV). All patients underwent 8 weeks of TNS, administered by the parents for 7–9 hours every night. Each child's device was set to provide stimulation that was perceptible but below the threshold of discomfort. Treatment adherence was measured with a parent-completed diary and by weekly interviews. The primary ADHD outcome measure was the ADHD-RS-IV, completed at weeks 4 and 8.

**Results:** A total of 24 children (mean age, 10 years) started TNS treatment. Two patients dropped out before week 4 and another before week 8, all for unknown reasons, resulting in a final sample size of 21 patients, all of whom completed treatment. Based on treatment diaries, nightly compliance was 100% in these 21 families. There were no reported problems with implementing TNS therapy.

After TNS treatment, patients demonstrated robust improvement in the investigator-rated ADHD-RS-IV and the parent-rated Conners Global Index (p<0.0001 for both). Improvements were evident for both the inattentive and hyperactive/impulsive subscales (p<0.0001 for each). The majority of patients (64%) were rated as improved or very much improved on the Clinical Global Impression–Improvement scale at week 4; this increased to 71% at week 8.
Although patients did not meet diagnostic criteria for depression, they did show dimensional-score improvement in depressive symptoms. They also improved in parent-reported executive functioning and some aspects of sleep.

No patient discontinued the study due to adverse events. Potentially treatment-related adverse events were transient headaches (n=2) and eye twitching (n=1), which resolved with no intervention and alternative placement of the electrodes, respectively.

McGough J, Loo S, Sturm A, Cowen J, et al: An eight-week, open-trial, pilot feasibility study of trigeminal nerve stimulation in youth with attention-deficit/hyperactivity disorder. Brain Stimulation 2014; doi 10.1016/j.brs.2014.11.013. From the University of California, Los Angeles. Funded by NeuroSigma, Inc.; and other sources. The authors did not include disclosure of potential conflicts of interest.

Early Intervention and Young Adult Psychopathology

In a randomized trial of high-risk young people, participation in a multicomponent intervention beginning in kindergarten was associated with lower rates of psychopathology, violent crime, and drug offenses at age 25 years.

Methods: The NIH-funded Fast Track prevention program was carried out at 4 sites in the U.S. beginning in 1991. Participants were “early starters”—i.e., children who showed evidence of antisocial development while in kindergarten. Participating elementary schools in poor, high-crime neighborhoods were randomly assigned to receive the Fast Track intervention or to act as controls. Nearly 10,000 kindergartners were evaluated for behavioral risk based on information from parents and teachers, and approximately 900 with the highest risk scores were enrolled in the trial and received either Fast Track or no intervention, based on the school they attended. The program was manualized, and a full description can be found at http://fasttrackproject.org. Interventions in elementary school were geared mostly toward improving peer interactions and social competence and included group training of parents, children, and parent-child pairs; tutoring; teacher involvement; and home visits. Additional training in middle and early high school focused on adolescent development, drugs and alcohol, and employment issues. Program participation ended with completion of the 10th grade. Data for the present analysis were obtained when participants were 25 years old and included administrative records and interviews with the participant and a peer of his or her choice. (Study results from earlier time points have been reported in several previous publications.) The analysis of outcomes was adjusted for 22 demographic, socioeconomic, and other variables that were measured prior to the intervention.

Results: Participants in the Fast Track program were less likely than their peers to have evidence of an internalizing, externalizing, or substance use disorder (odds ratio,* 0.59; p=0.001). This result was consistent in separate analyses of all subgroups evaluated: males and females, high- and moderate-risk individuals, those racially identified as African- or European-Americans, and those at all 4 study sites. The number needed to treat* for prevention of 1 case of a psychiatric disorder was 8. Intervention decreased the rate of violent crime convictions by 31% and that of drug convictions by 35%. Fast Track participants were less likely to engage in risky sexual behavior and to spank their own children. The program was associated with higher self-ratings of well-being, but not general health or personal strength. Also unaffected were educational attainment and employment.

Dodge K, Bierman K, Coie J, Greenberg M, et al: Impact of early intervention on psychopathology, crime, and well-being at age 25. American Journal of Psychiatry 2015;172 (January):59–70. From Duke University, Durham, NC; and other institutions. Funded by the NIMH; and other sources. Six study authors declared financial relationships with commercial sources; the remaining authors declared no conflicts of interest.

*See Reference Guide.
Antidepressant Monotherapy and Manic Switching

In a group of children and adolescents with bipolar depression, antidepressant monotherapy was associated with an increased risk of manic switching compared with second-generation antipsychotic monotherapy. No difference in risk was found between antidepressant monotherapy and mood stabilizer monotherapy, or between antidepressant polytherapy (i.e., antidepressant with either an antipsychotic or a mood stabilizer) and antipsychotic–mood stabilizer combinations.

Methods: A cohort of patients, aged 6–18 years, receiving treatment for bipolar depression between 2003 and 2007 was assembled using Medicaid claims data from 4 large states. The 4147 patients were divided into 5 mutually exclusive treatment groups based on their medication during the 30 days surrounding the index diagnosis of bipolar depression: antidepressant monotherapy (n=179); antipsychotic monotherapy (n=1047); mood stabilizer monotherapy (n=570); antidepressant polytherapy (n=445); and antipsychotic–mood stabilizer polytherapy (n=1906). Manic switch was identified as treatment-emergent if it occurred within 6 weeks after the initiation of bipolar depression treatment.

Results: During follow-up, rates of manic switch ranged from 8% to 11% across the treatment groups. After controlling for all observable confounders (e.g., demographics, comorbid conditions, physician factors), antidepressant monotherapy was associated with a higher rate of manic switching than antipsychotic monotherapy (hazard ratio,* 2.87). Risk was numerically, but not statistically, higher with antidepressant monotherapy versus mood stabilizer monotherapy and with antidepressant polytherapy versus antipsychotic–mood stabilizer therapy. In all analyses, a history of a prior manic episode was by far the strongest predictor of a manic switch (hazard ratio, 14).

Discussion: Based in part on the belief that childhood-onset bipolar disorder is more severe and volatile than the adult-onset form, pediatric guidelines are more conservative in recommending the use of antidepressants. Adjunctive antidepressant use is common in young patients with bipolar disorder, but antidepressant monotherapy is not, according to prior research. The results of the present study, the first to assess risk of manic switching in children and adolescents, support the belief that a concomitant antipsychotic or mood stabilizer can reduce the risk of antidepressant-induced manic switching.

Study Rating*—12 (86%): This study met most criteria for an observational study, but the source of funding was not stated.

Bhowmik D, Aparasu R, Rajan S, Sherer J, et al: Risk of manic switch associated with antidepressant therapy in pediatric bipolar depression. Journal of Child and Adolescent Psychopharmacology 2014;24 (December):551–561. From the College of Pharmacy, University of Houston, TX; and other institutions. Source of funding not stated. The authors declared no conflicts of interest.

*See Reference Guide.

Predictors of Suicidal Behavior in ADHD

In adolescents with ADHD, suicidal behavior was linked with several modifiable risk factors in a cross-sectional study. The factors—depression, parent-child conflict, victimization trauma, and social impairment—may be useful in identifying young people at risk for suicide and could be targets for psychosocial or pharmacological interventions.

Methods: Study participants were 101 adolescents, aged 11–18 years, enrolled in a longitudinal study of depression risk factors in ADHD. All participants met DSM-IV-TR diagnostic criteria for ADHD. As part of the larger study, patients underwent a baseline assessment that provided
data for the present analysis. Adolescents and their parents underwent separate interviews with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL). Suicidal behavior was defined as suicidal gestures, suicide attempts, or self-injurious behaviors carried out in the presence of suicidal ideation. These behaviors were identified by interviewers after weighing information from both the adolescent and the parent and resolving any conflicts in an individualized manner. Potential correlates of lifetime suicidal behaviors were measured using the KSADS-PL and other standardized rating scales.

**Results:** The final sample included 37 girls and 64 boys; 31 reported lifetime suicidal ideation. Of these, 28 reported lifetime suicidal behaviors. Adolescents with suicidal behavior were older, were more likely to be female, and had a higher lifetime prevalence of depressive, externalizing, or substance use disorders than the rest of the sample. They also had higher levels of functional impairment, particularly in the areas of peer and family relationships, interest and activities, and parent-child conflict. Suicidal behavior was also associated with trauma based on victimization events; specifically, adolescents who engaged in suicidal behavior were more likely to have experienced domestic violence or physical abuse or to have been kidnapped by a noncustodial parent. They were also more likely to have had a psychiatric hospitalization or to have received antidepressant medication. Contrary to the investigators’ expectation, adolescents with suicidal behavior did not have increased ADHD severity.

In a multivariate analysis, several variables remained associated with suicidal behavior after adjusting for age, gender, and lifetime diagnosis of major depressive, externalizing, or substance-use disorders. Depression remained the strongest multivariate risk factor, with an odds ratio,* of 7.0 (p=0.001). The remaining factors were parent-child conflicts (odds ratio, 3.2; p=0.003) and the number of victimization events (odds ratio, 1.4; p=0.03).

**Discussion:** The association of depression with suicidal behavior in adolescents with ADHD is well known. The present results indicate that potentially modifiable environmental factors and impairment are additional predictors of suicidal behavior. These factors could be targeted with pharmacological or psychosocial treatments to lessen risk of suicide in patients with ADHD.

Daviss W, Diler R: Suicidal behaviors in adolescents with ADHD: associations with depressive and other comorbidity, parent-child conflict, trauma exposure, and impairment. *Journal of Attention Disorders* 2014;18 (November):680–690. From the University of Pittsburgh, PA; and Geisel School of Medicine at Dartmouth, Hanover, NH. **Funded by the National Alliance for Research on Schizophrenia and Depression; and the NIMH. One study author declared financial relationships with commercial sources; the remaining author declared no conflicts of interest.**

*See Reference Guide.

**Web-Based Interventions for Depression, Anxiety**

According to results of a systematic review, evidence for the effectiveness of web-based or mobile interventions for young people with internalizing problems is limited. However, the limited evidence suggests they may be viewed as a gateway or an adjunct to, rather than a replacement for, face-to-face treatment.

**Methods:** A comprehensive literature search was undertaken in order to gather information published since 2009 when a previous review was conducted. Included articles were English-language reports, published or unpublished, that became available between 2000 and 2013. The review’s focus was internet-based interventions and mobile apps designed to prevent or treat symptoms of anxiety or depression or for suicide prevention in children (aged 5–12 years), adolescents (aged 13–17 years), and/or emerging adults (aged 18–25 years). The review excluded case series and studies of virtual-reality exposure treatments or messaging-only apps. Study outcomes were estimated using effect size.* See table (next page) for intervention details.
<table>
<thead>
<tr>
<th>Program</th>
<th>Description</th>
<th>Structure</th>
<th>Clinician Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATCH-IT</td>
<td>Based on CBT and interpersonal therapy; designed to prevent or reduce depressive symptoms</td>
<td>14 sequential modules, includes skill-building exercises, feedback, and internet-based rewards</td>
<td>Self-guided; enhanced versions can include motivational interviewing or brief advice</td>
</tr>
<tr>
<td>Master Your Mood (MYM)</td>
<td>Based on CBT for youth with depressive symptoms</td>
<td>6 weekly sessions (90 min each) with a chat room-based presentation, includes psychoeducation, self-monitoring, cognitive restructuring, participation in pleasant activities, and relapse prevention</td>
<td>Therapist-assisted</td>
</tr>
<tr>
<td>MoodHelper</td>
<td>CBT-based intervention for young adults with depression</td>
<td>4-modules: graphically-displayed depression scale, journal, interactive tutorials, cognitive restructuring tool</td>
<td>Self-guided</td>
</tr>
<tr>
<td>Feeling Better</td>
<td>CBT-based internet intervention designed to reduce depression, anxiety, and stress in college students with mild-to-moderate symptoms</td>
<td>11 modules: 4 core skills delivered in 7 sequential modules plus 4 optional modules, core skills: psychoeducation, goal-setting, cognitive restructuring, stress management, optional: sleep hygiene, anger management, review of nonpsychological treatments, premenstrual syndrome, and mood</td>
<td>Minimal therapist assistance</td>
</tr>
<tr>
<td>Mobiletype</td>
<td>The only identified mobile app; designed to help clinicians identify and manage depression, anxiety, and stress in college students</td>
<td>Self-monitoring of activities, mood, stress, alcohol and cannabis use, sleep, exercise, and diet, random prompts to complete self-monitoring entries</td>
<td>Physician-review upon completion</td>
</tr>
<tr>
<td>MoodGYM</td>
<td>CBT-based intervention adapted from an adult program for use by adolescents to treat or prevent depression</td>
<td>5 sessions (30–60 min each) that include animated demos, quizzes, and homework covering relaxation, problem solving, cognitive restructuring, assertiveness, self-esteem, and relationships</td>
<td>Self-guided</td>
</tr>
<tr>
<td>Problem-Solving Therapy</td>
<td>CBT-based internet program aimed at preventing adolescent depression and anxiety</td>
<td>5 weekly sessions focused on problem solving, strategies to eliminate negative thoughts and enhance positive thoughts, and goal setting</td>
<td>Minimal therapist assistance</td>
</tr>
<tr>
<td>PST</td>
<td>CBT-based internet intervention for youth with established separation anxiety disorder, generalized anxiety disorder, social or specific phobia</td>
<td>10 weekly sessions (60 min each) using real-life examples, games, quizzes, and homework to cover psychoeducation, relaxation strategies, cognitive restructuring, graded exposure, and problem solving, 2 booster sessions after completion, 5 parent sessions focused on psychoeducation, contingency management, relaxation training, and anxiety management strategies</td>
<td>Minimal therapist assistance</td>
</tr>
<tr>
<td>BRAVE ONLINE</td>
<td>CBT-based, internet intervention for youth with established separation anxiety disorder, generalized anxiety disorder, social or specific phobia</td>
<td>5 weekly sessions focused on problem solving, strategies to eliminate negative thoughts and enhance positive thoughts, and goal setting</td>
<td>Minimal therapist assistance</td>
</tr>
<tr>
<td>Cognitive Bias Modification</td>
<td>Internet-delivered, attention bias modification program for youth with symptoms of social phobia and test anxiety</td>
<td>20 sessions (40 min twice weekly) focused on imagination training, ambiguous social situations, and visual probes</td>
<td>Self-guided</td>
</tr>
</tbody>
</table>
**Results:** The authors identified 25 articles describing 9 programs: 8 web-based and 1 mobile app. A total of 14 studies were randomized controlled trials, and the rest were open studies, follow-up studies, and secondary-data analyses. Sample sizes ranged from 14 to >8000. Of the 9 programs, 3 were for depression, 2 for anxiety, and 4 for either problem; no programs for suicide prevention were identified. All programs were based on cognitive behavioral therapy (CBT).

The BRAVE ONLINE program was the only intervention with sufficient evidence to classify it as probably efficacious. MoodGym and MYM were judged possibly efficacious; CATCH-IT, Feeling Better, and MoodHelper were deemed experimental; and PST, Mobiletype, and CBM were considered of questionable efficacy. BRAVE ONLINE is the only program developed for patients with a full diagnosis, rather than a high-risk group or one with sub-threshold symptoms. It has been the subject of 3 randomized controlled trials, which reported moderate-to-large effect sizes. However, a major limitation of the evidence is that all of the studies were conducted by the programs’ developers.


From the New York State Psychiatric Institute, Columbia University Medical Center, New York, NY. Funded by the Sallie Foundation Child and Adolescent Mental Health Technology Program. Six study authors declared financial relationships with commercial sources; the remaining author declared no conflicts of interest.

*See Reference Guide.*

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance and large effect sizes do not ensure treatment efficacy.

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

**Number Needed to Treat:** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

**Odds Ratio:** A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.